

WHAT IS CLAIMED IS:

- 1 1. A method for counteracting a pathologic change in a signal-transduction
2 pathway involving a member of the steroid/thyroid hormone super-family, comprising
3 administering to a mammalian subject in need an effective amount of a compound capable of
4 inhibiting TGF- β signaling through a TGF- β receptor.
- 1 2. The method of claim 1 wherein the receptor is a steroid hormone receptor.
- 1 3. The method of claim 2 wherein the pathologic change is down- or up-
2 regulation of the steroid hormone receptor.
- 1 4. The method of claim 3 wherein the down- or up-regulation involves TGF- β .
- 1 5. The method of claim 3 wherein the down- or up-regulation is induced by
2 TGF- β .
- 1 6. The method of claim 1 wherein the pathologic change is a TGF- β induced
2 change in the activity or signaling of a steroid hormone receptor.
- 1 7. The method of claim 2 wherein the steroid hormone receptor is glucocorticoid
2 receptor.
- 1 8. The method of claim 1 wherein the receptor is a thyroid hormone receptor.
- 1 9. The method of claim 8 wherein the pathologic change is down- or up-
2 regulation of a thyroid hormone receptor.
- 1 10. The method of claim 9 wherein the down- or up-regulation involves TGF- β .
- 1 11. The method of claim 9 wherein the down- or up-regulation is induced by
2 TGF- β .

3 12. The method of claim 8 wherein the pathologic change is a TGF- β induced
4 change in the activity or signaling of a thyroid hormone receptor.

1 13. The method of claim 1 wherein the receptor is a retinoic acid receptor.

1 14. The method of claim 13 wherein the pathologic change is down- or up-
2 regulation of a retinoic acid receptor.

1 15. The method of claim 14 wherein the down- or up-regulation involves TGF- β .

1 16. The method of claim 14 wherein the down- or up-regulation is induced by
2 TGF- β .

1 17. The method of claim 13 wherein the pathologic change is a TGF- β induced
2 change in the activity or signaling of a retinoic acid receptor.

1 18. The method of claim 1 wherein the TGF- β receptor is a TGF β -R1 kinase.

1 19. The method of claim 18 wherein the compound is capable of binding to said
2 TGF β -R1 kinase.

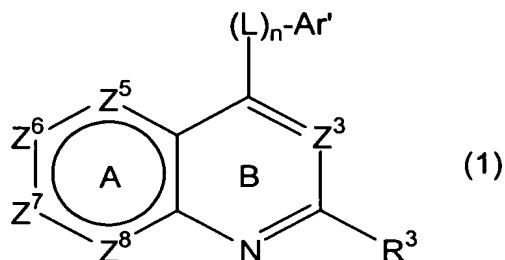
1 20. The method of claim 19 wherein the compound is capable of binding to an
2 additional receptor kinase.

1 21. The method of claim 20 wherein the additional receptor kinase is an activin
2 receptor (Alk4).

1 22. The method of claim 1 wherein the compound is a non-peptide small
2 molecule.

1 23. The method of claim 22 wherein the compound is a small organic molecule.

1 24. The method of claim 23 wherein the small organic molecule is a compound of
2 formula (1)



3 or the pharmaceutically acceptable salts thereof
4 wherein R³ is a noninterfering substituent;
5 each Z is CR² or N, wherein no more than two Z positions in ring A are N, and
6 wherein two adjacent Z positions in ring A cannot be N;
7 each R² is independently a noninterfering substituent;
8 L is a linker;
9 n is 0 or 1; and
10 Ar' is the residue of a cyclic aliphatic, cyclic heteroaliphatic, aromatic or
11 heteroaromatic moiety optionally substituted with 1-3 noninterfering substituents.

1 25. The method of claim 24 wherein the compound is a quinazoline derivative.

1 26. The method of claim 25 wherein Z³ is N; and Z⁵-Z⁸ are CR².

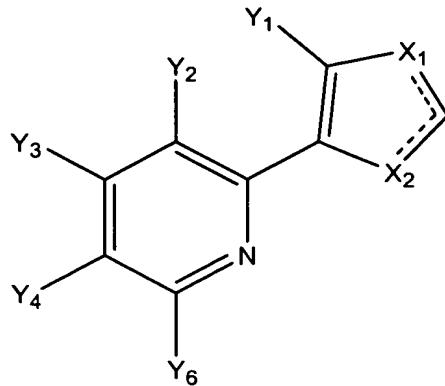
1 27. The method of claim 25 wherein Z³ is N; and at least one of Z⁵-Z⁸ is nitrogen.

1 28. The method of claim 25 wherein R³ is an optionally substituted phenyl moiety.

1 29. The method of claim 28 wherein R³ is selected from the group consisting of 2-
2 4-, 5-, 2,4- and 2,5-substituted phenyl moieties.

1 30. The method of claim 29 wherein at least one substituent of the phenyl moiety
2 is an alkyl(1-6C), or halo.

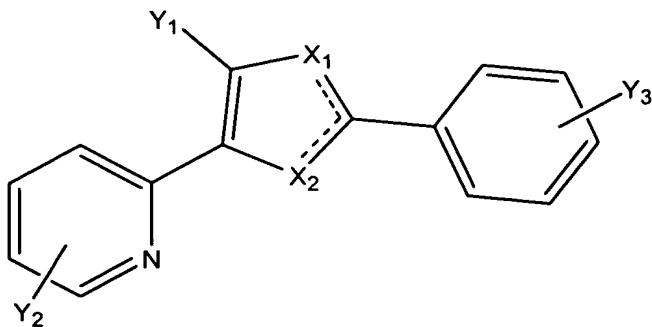
1 31. The method of claim 23, wherein the small organic molecule is a compound of
2 formula (2)



3 wherein Y₁ is phenyl or naphthyl optionally substituted with one or more
4 substituents selected from halo, alkoxy(1-6 C), alkylthio(1-6 C), alkyl(1-6 C), haloalkyl (1-
5 6C), -O-(CH₂)_m-Ph, -S-(CH₂)_m-Ph, cyano, phenyl, and CO₂R, wherein R is hydrogen or
6 alkyl(1-6 C), and m is 0-3; or phenyl fused with a 5- or 7-membered aromatic or non-
7 aromatic ring wherein said ring contains up to three heteroatoms, independently selected
8 from N, O, and

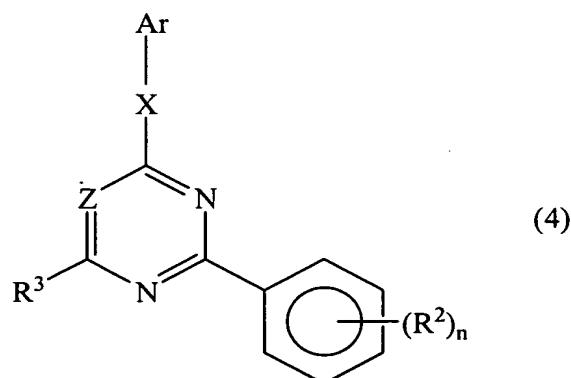
9 Y₂, Y₃, Y₄, and Y₅ independently represent hydrogen, alkyl(1-6C), alkoxy(1-6
10 C), haloalkyl(1-6 C), halo, NH₂, NH-alkyl(1-6C), or NH(CH₂)_n-Ph wherein n is 0-3; or an
11 adjacent pair of Y₂, Y₃, Y₄, and Y₅ form a fused 6-membered aromatic ring optionally
12 containing up to 2 nitrogen atoms, said ring being optionally substituted by one or more
13 substituents independently selected from alkyl(1-6 C), alkoxy(a-6 C), haloalkyl(1-6 C), halo,
14 NH₂, NH-alkyl(1-6 C), or NH(CH₂)_n-Ph, wherein n is 0-3, and the remainder of Y₂, Y₃, Y₄,
15 and Y₅ represent hydrogen, alkyl(1-6 C), alkoxy(1-6C), haloalkyl(1-6 C), halo, NH₂, NH-
16 alkyl(1-6 C), or NH(CH₂)_n-Ph wherein n is 0-3; and
17 one of X₁ and X₂ is N and the other is NR₆, wherein R₆ is hydrogen or alkyl(1-
18 6 C).

1 32. The method of claim 23 wherein the small organic molecule is a compound of
2 formula (3)



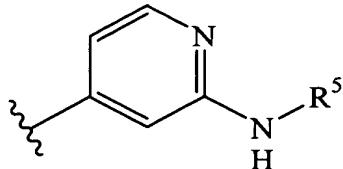
3 wherein Y_1 is naphthyl, anthracenyl, or phenyl optionally substituted with one
 4 or more substituents selected from the group consisting of halo, alkoxy(1-6 C), alkylthio(1-6
 5 C), alkyl(1-6 C), $-O-(CH_2)_n-Ph$, $-S-(CH_2)_n-Ph$, cyano, phenyl, and CO_2R , wherein R is
 6 hydrogen or alkyl(1-6 C), and n is 0, 1, 2, or 3; or Y_1 represents phenyl fused with an
 7 aromatic or non-aromatic cyclic ring of 5-7 members wherein said cyclic ring optionally
 8 contains up to two heteroatoms, independently selected from N, O, and S;
 9 Y_2 is H, $NH(CH_2)_n-Ph$ or NH -alkyl(1-6 C), wherein n is 0, 1, 2, or 3;
 10 Y_3 is CO_2H , $CONH_2$, CN , NO_2 , alkylthio(1-6 C), $-SO_2$ -alkyl(C1-6),
 11 alkoxy(C1-6), $SONH_2$, $CONHOH$, NH_2 , CHO , CH_2NH_2 , or CO_2R , wherein R is hydrogen or
 12 alkyl(1-6 C);
 13 one of X_1 and X_2 is N or CR' , and other is NR' or CHR' wherein R' is
 14 hydrogen, OH, alkyl(C-16), or cycloalkyl(C3-7); or when one of X_1 and X_2 is N or CR' then
 15 the other may be S or O.

1 33. The method of claim 23 wherein the small organic molecule is a compound of
 2 formula (4)



3 and the pharmaceutically acceptable salts and prodrug forms thereof; wherein

4 Ar represents an optionally substituted aromatic or optionally substituted
5 heteroaromatic moiety containing 5-12 ring members wherein said heteroaromatic moiety
6 contains one or more O, S, and/or N with a proviso that the optionally substituted Ar is not



7 wherein R⁵ is H, alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), an aromatic or
8 heteroaromatic moiety containing 5-11 ring members;

9 X is NR¹, O, or S;

10 R¹ is H, alkyl (1-8C), alkenyl (2-8C), or alkynyl (2-8C);

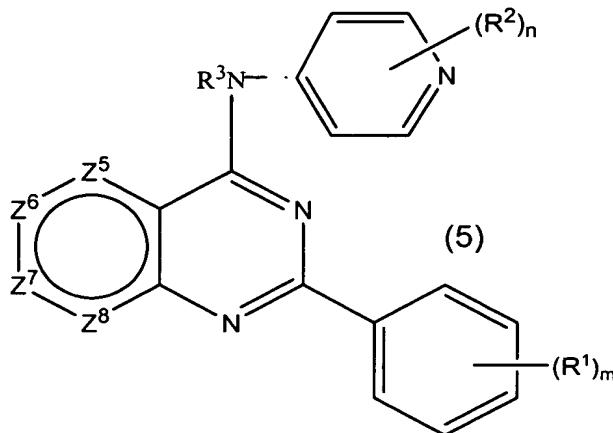
11 Z represents N or CR⁴;

12 each of R³ and R⁴ is independently H, or a non-interfering substituent;

13 each R² is independently a non-interfering substituent; and

14 n is 0, 1, 2, 3, 4, or 5. In one embodiment, if n>2, and the R²'s are adjacent,
15 they can be joined together to form a 5 to 7 membered non-aromatic, heteroaromatic, or
16 aromatic ring containing 1 to 3 heteroatoms where each heteroatom can independently be O,
17 N, or S.

1 34. The method of claim 23 wherein the small organic molecule is a compound of
2 formula (5)



3 or the pharmaceutically acceptable salts thereof;

4 wherein each of Z⁵, Z⁶, Z⁷ and Z⁸ is N or CH and wherein one or two Z⁵, Z⁶,

5 Z⁷ and Z⁸ are N and wherein two adjacent Z positions cannot be N;

6 wherein m and n are each independently 0-3;
7 wherein two adjacent R¹ groups may be joined to form an aliphatic
8 heterocyclic ring of 5-6 members;
9 wherein R² is a noninterfering substituent; and
10 wherein R³ is H or CH₃.